

Amendments to the Specification:

Please replace the title on page 1 with the following replacement title:

A Method of Purifying Factor VIII/vWF Complex by Means
of Cation Exchange Chromatography
Factor VIII/vWF Complexes and Compositions

Please replace the paragraph that was added as a new first paragraph in the amendment submitted on November 2, 2001, with the following rewritten paragraph:

CROSS REFERENCE TO RELATED APPLICATIONS

This is a divisional of U.S. Patent Application Serial No. 09/367,459, filed May 8, 2000, (incorporated herein by reference in its entirety), which is a national phase of PCT Patent Application No. PCT/AT98/00043, filed February 27 1998, which claims priority to ~~AT Austrian Patent Application No. A338/97 filed February 27, 1997, all of which are incorporated herein by reference in their entirety.~~

Please replace the first paragraph on page 1 with the following rewritten paragraph by adding the section heading as indicated below:

FIELD OF THE INVENTION

The invention relates to a method of purifying factor VIII/vWF-complex from a biological starting material by means of cation exchange chromatography and step-wise elution, as well as purified factor VIII/vWF-complex which particularly comprises high-molecular vWF multimers.

Please replace the second paragraph on page 1 with the following rewritten paragraph by adding the section heading as indicated below:

BACKGROUND

von Willebrand factor circulates in plasma at a concentration of from 5 to 10 mg/l, mainly in the form of a non-covalently bound complex with factor VIII. In the cryoprecipitate, factor VIII/vWF-complex is highly enriched and can be isolated therefrom or from plasma or from plasma fractions by means of known fractionation methods.

Please replace the second paragraph on page 4 with the following rewritten paragraph by adding the indicated section heading:

SUMMARY

Thus, it is the object of the present invention to provide a factor VIII/vWF complex having improved specific activity and stability.

Please insert the following new section after the third paragraph on page 4:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a vWF multimer analysis of factor VIII/vWF-complex from cryoprecipitate, before and after purification with cation exchanger.

Fig. 2 shows a vWF multimer analysis of factor VIII/vWF-complex from cryoprecipitate, before and after purification by means of a combined anion/cation exchange chromatography.

Please replace the paragraph beginning on page 7, line 3 with the following rewritten paragraph:

Every known cation exchanger can be used for carrying out this method, cation exchangers having a sulfopropyl- or carboxymethyl-group conjugated carrier being preferred. SP-Sephadex~~SEPHAROSE~~® Fast Flow and CM-Sephadex~~SEPHAROSE~~® Fast Flow (Pharmacia), Fractogel~~FRACTOGEL~~® EMD-SO₃ and Fractogel~~FRACTOGEL~~® EMD COOH (Merck), Porous~~POROUS~~® 10 SP and Poros~~POROUS~~® 10S (Perseptive Biosystems) and Toyopearl~~TOYOPEARL~~™ SP 550 C and Toyopearl~~TOYOPEARL~~™ CM-650 (M) (TosoHaas) have, e.g., proved to be well suitable.

Please replace the first full paragraph on page 17 with the following rewritten paragraph:

The invention will now be explained in more detail by way of the following examples and the drawing figures, examples; however, it shall not be restricted to these exemplary embodiments.

Please delete the paragraph beginning on page 17, line 20 (i.e., the paragraph regarding Fig. 1).

Please delete the paragraph beginning on page 17, line 23 (i.e., the paragraph regarding Fig. 2).

Please replace the last paragraph on page 24 with the following rewritten paragraph:

1000 ml of a cell culture supernatant containing recombinant rFVIII/rvWR-complex were was applied onto a column filled with 20 ml of Fraetogel FRACTOGEL® TSK-SO3. After having washed the column with buffer, pH 7.4, with 250 mM NaCl, the bound rFVIII/rvWF-complex was eluted by means of a buffer, pH 7.4, with 600 mM NaCl. In Table 4 the results of this column run are illustrated.

Please replace the section beginning on page 27, line 1 with the following rewritten section:

Example 4B

In this Example, Toyopearl TOYOPEARL™ SP-550C was used instead of Fraetogel FRACTOGEL® EMD-SO₃.